Tetrahedron Letters 51 (2010) 6444–6446

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Studies directed toward the synthesis of rhizopodin: stereoselective synthesis of the C1–C15 fragment ☆

Tushar Kanti Chakraborty [a,*], Kiran Kumar Pulukuri [a], Midde Sreekanth [b]

[a] Central Drug Research Institute, CSIR, Lucknow 226001, India
[b] Indian Institute of Chemical Technology, CSIR, Hyderabad 500607, India

ARTICLE INFO

Article history:
Received 3 September 2010
Revised 27 September 2010
Accepted 29 September 2010
Available online 7 October 2010

Keywords:
Rhizopodin
Acetate aldol reaction
Keck allylation
Stille coupling

ABSTRACT

A stereoselective synthesis of the C1–C15 fragment of a G-actin binding natural macrodiolide, rhizopodin was achieved using, as key steps, highly stereoselective acetate aldol reactions to build the C1–C7 fragment, one pot oxazole synthesis and an asymmetric Keck allylation reaction to build the C8–C15 fragment and finally, a Stille reaction to couple both the fragments.

Rhizopodin (**1**) is a novel polyketide isolated from the myxobacterium *Myxococcus stipitatus*.[1] Based on the crystal structure of rhizopodin—G-actin complex, its structure was identified as a C_2-symmetric, 38-membered dilactone having 18 chiral centers, two disubstituted oxazole rings, and two conjugated diene systems.[2] Rhizopodin has been found to dramatically affect the cytoskeleton of eukaryotic cells even at nanomolar concentrations, an ability traced to its property of binding there by inhibiting the polymerization of actin.[2,3] Unlike other dimeric macrolides with actin polymerization inhibitory activity like swinholides, misakinolide A, and bisteonelide B, rhizopodin behaves as a bivalent inhibitor forming a ternary complex with the two actin molecules.[2] The challenging structure of the molecule coupled with its unique biological activities prompted us to undertake its total synthesis. A stereoselective synthesis of the C9–C23 fragment has been reported.[4] In this Letter, we report the stereoselective synthesis of the C1–C15 fragment of the molecule.

The retrosynthetic analysis of rhizopodin (**1**) is outlined in Scheme 1. A sequential esterification/macrolactonization or cyclodimerization was contemplated to construct the macrocyclic ring from the suitably protected monomeric hydroxyl acid **2**. We envisaged that the two halves of the monomer, the C1–C15 unit **3** and the C16–C28 unit **4**, could be combined by a Nozaki–Hiyama–Kishi reaction[5] to obtain the entire length of C1–C28 of the monomer.

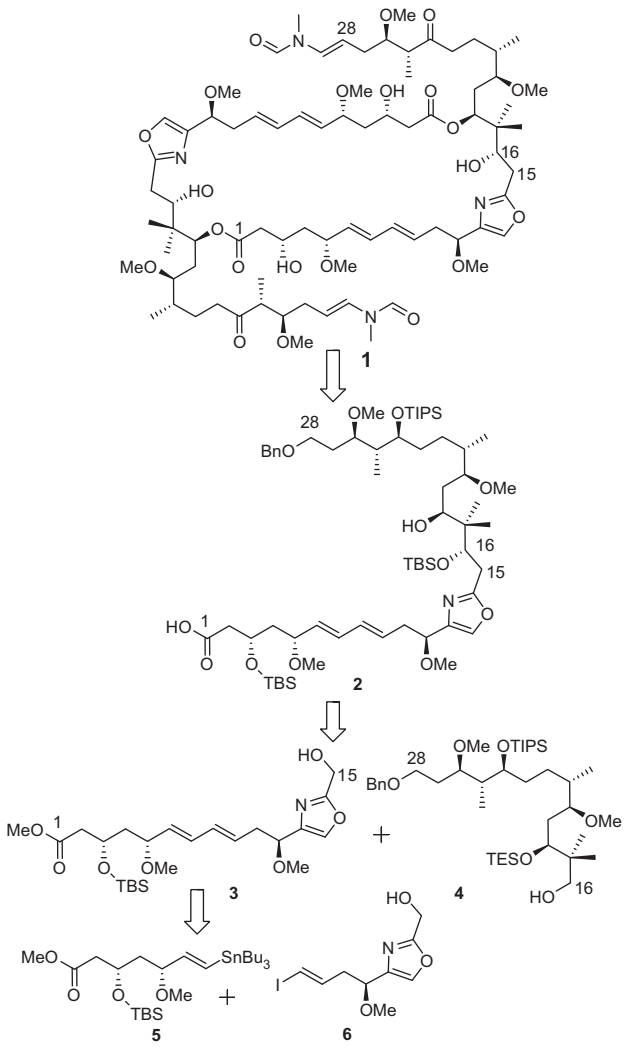
Schemes 2–4 outlines the synthesis of the first C1–C15 fragment **3**. The synthesis of vinyl stannane (Scheme 2) was started with cinnamaldehyde dimethyl acetal **7** which was prepared from *trans*-cinnamaldehyde following standard procedures.[6] An acetal aldol reaction of dimethyl-acetal **7** with (*R*)-*N*-acetyl-4-isopropyl-1,3-thiozolidine-2-thione **8** according to the conditions described by Urpi[7] provided the aldol products in 91% yield in 4:1 diastereomeric ratio. The required, diastereomerically pure product **9** could be easily separated through silica gel column chromatography.[8] Reductive cleavage of the chiral auxiliary using DIBAL-H afforded aldehyde **10** in 92% yield, which was subjected to an acetate aldol reaction with (*S*)-*N*-acetyl-4-isopropyl-1,3-thiozolidine-2-thione **11** to afford the desired alcohol **12** in 84% yield and 14:1 diastereomeric ratio.[10] Removal of the chiral auxiliary using imidazole in MeOH afforded the methyl ester **13** in 92% yield.[11] Protection of the hydroxy group of **13** using TBSOTf and 2,6-lutidine afforded the TBS protected compound **14** in 96% yield. The cinnamyl moiety was transformed to vinylstannane by oxidation of the olefin using OsO_4 and NMO followed by oxidative cleavage to afford the aldehyde **15** in 90% yield. The resultant aldehyde was transformed to alkyne **17** using Bestmann–Ohira reagent **16** in 72% yield.[12] Hydrostannyllation of alkyne with $Pd(PPh_3)_2Cl_2$ and *n*-Bu_3SnH afforded the *E*-vinylstannane **5** in 76% yield.[13]

For the preparation of the vinyl iodide–oxazole fragment **6** (Scheme 3), coupling of *p*-methoxybenzyloxyacetic acid **18** with

☆ CDRI Communication No. 7964.

* Corresponding author. Tel.: +91 522 2623286; fax: +91 522 2623405/3938.
E-mail address: chakraborty@cdri.res.in (T.K. Chakraborty).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.09.144



Scheme 1. Retrosynthetic analysis of rhizopodin (**1**).

DL-serine methyl ester hydrochloride **19** using ethyl chloroformate and *N*-methylmorpholine afforded the amide **20** in 74% yield.[14] The resultant amide was converted to the oxazole **21** in one pot following the Wipf and Williams[15] methodology with Deoxo-Fluor, bromochloroform, and DBU to afford **21** in 70% yield. Reduction of oxazole ester using DIBAL-H at −80 °C afforded the aldehyde **22** in 90% yield.[16] Asymmetric allylation of aldehyde with (*S*)-BINOL, $Ti(O^iPr)_4$, and allyl tributylstannane afforded the allylic alcohol **23** in 87% yield with 94% ee.[17] Methylation of hydroxyl with NaH and iodomethane in DMF afforded the methyl ether **24** in 83% yield. Dihydroxylation of the double bond followed by oxidative cleavage using sodium periodate furnished the aldehyde **25** in 84% yield. The aldehyde **25** was converted to dibromoalkene **26**, using TPP, CBr_4, and triethylamine, which was next transformed into alkynyl bromide **27** using NaHMDS.[18] One pot hydrostannylation–iodination of **27** produced *E*-vinyl iodide **28** in 84% yield.[19] Oxidative removal of PMB group with DDQ afforded the desired C8–C15 fragment **6** in 94% yield.[20]

With the requisite C1–C7 and C8–C15 fragments in hand, their coupling was undertaken next as shown in Scheme 4. This was done using Stille coupling[21] conditions in the presence of *bis*-acetonitrile palladium(II) chloride complex in DMF to give the desired *E*,*E*-diene **3** in 54% yield.[22]

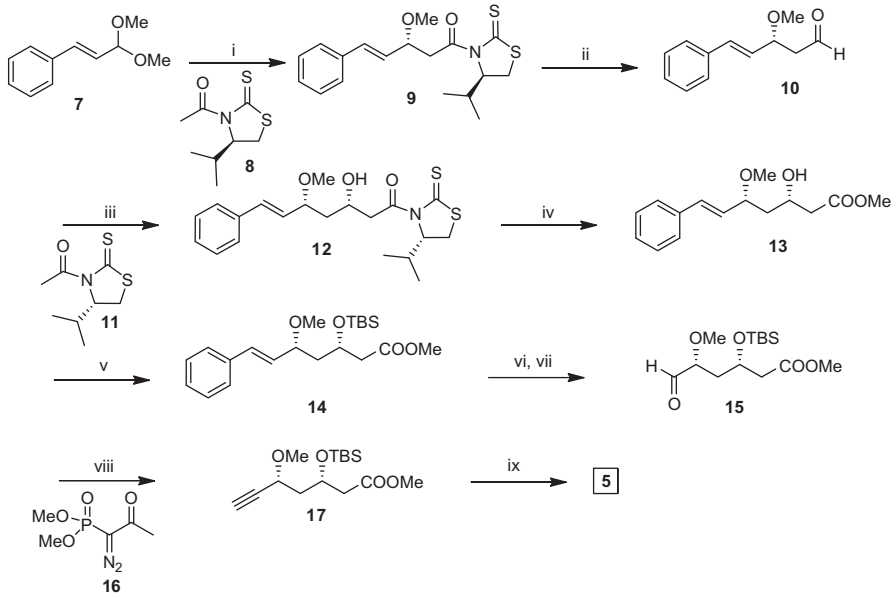
In summary, we have achieved a highly stereoselective convergent synthesis of the C1–C15 fragment of rhizopodin. Further work toward the total synthesis of the molecule is currently in progress.

Acknowledgments

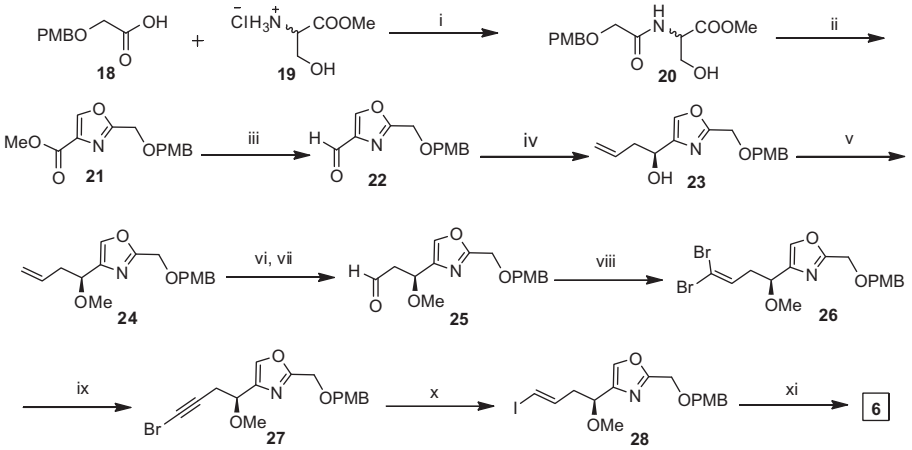
The authors wish to thank the CSIR, New Delhi for a research fellowship (P.K.K. and M.S.) and the SAIF, CDRI for providing the spectroscopic and analytical data.

Supplementary data

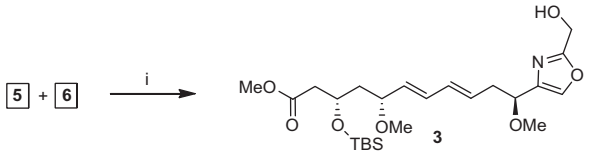
Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.144.



Scheme 2. Synthesis of **5**. Reagents and conditions: (i) $TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, −50 °C, 2 h, BF_3Et_2O, −78 °C, 10 min, 71%; (ii) DIBAL-H, −78 °C, CH_2Cl_2, 30 min, 92%; (iii) $Sn(OTf)_2$, *N*-ethylpiperidine, CH_2Cl_2, −50 °C, 8 h, 84%; (iv) Imidazole , methanol, rt, 12 h, 92%; (v) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 10 min, 96%; (vi) OsO_4, acetone/H_2O (8:1), rt, 4 h; (vii) $NaIO_4$, THF: pH 7 buffer (1:1), 0 °C to rt, 0.5 h, 90% after two steps; (viii) K_2CO_3, methanol, 0 °C to rt, 4 h, 72%; (ix) $PdCl_2(PPh_3)_2$, *n*-Bu_3SnH, CH_2Cl_2, 0 °C, 0.5 h, 76%.



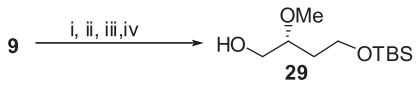
Scheme 3. Synthesis of **6**. Reagents and conditions: (i) Ethyl chloroformate, NMM, CH_2Cl_2, −20–0 °C, 12 h, 74%; (ii) Deoxo-Fluor, −20 °C, 0.5 h, $BrCCl_3$, DBU, 0 °C, CH_2Cl_2, 8 h, 70%; (iii) DIBAL-H, −80 °C, CH_2Cl_2, 20 min, 90%; (iv) (*S*)-BINOL, $Ti(O^iPr)_4$, allyl tributylstannane, CH_2Cl_2, −20 °C, 72 h, 87%, 94% ee; (v) NaH, MeI, DMF, 0 °C, 4 h, 83%; (vi) OsO_4, acetone/H_2O (8:1), rt, 2 h; (vii) $NaIO_4$, THF/H_2O (1:1), 0 °C , 1 h, 84% after two steps; (viii) PPh_3, CBr_4, NEt_3, CH_2Cl_2, 0 °C, 0.5 h, 92%; (ix) NaHMDS, −78 °C, THF, 2 h, 78%; (x) $PdCl_2(PPh_3)_2$, *n*-Bu_3SnH, THF, 0 °C, 2 h, then I_2, 0 °C, 0.5 h, 84%; (xi) DDQ, $CHCl_3/H_2O$ 20:1, 0 °C, 3 h, 94%.



Scheme 4. Synthesis of **3**. Reagents and conditions: (i) $PdCl_2(CH_3CN)_2$, DMF, rt, 54%.

References and notes

1. Sasse, F.; Steinmetz, H.; Hofle, G.; Reichenbach, H. *J. Antibiot.* **1993**, *46*, 741–748.
2. (a) Hagelueken, G.; Albrecht, S. C.; Steinmetz, H.; Jansen, R.; Heinz, D. W.; Kalesse, M.; Schubert, W. D. *Angew. Chem. Int. Ed.* **2009**, *48*, 595–598; (b) Horstmann, N.; Menche, D. *Chem. Commun.* **2008**, 5173–5175; (c) Jansen, R.; Steinmetz, H.; Sasse, F.; Schubert, W. D.; Hagelueken, G.; Muller, R. *Tetrahedron Lett.* **2008**, *49*, 5796–5799.
3. Gronewold, T. M. A.; Sasse, F.; Lunsdorf, H.; Reichenbach, H. *Cell Tissue Res.* **1999**, *295*, 121–129.
4. Chen, Z.; Song, L.; Xu, Z.; Ye, T. *Org. Lett.* **2010**, *12*, 2036–2039.
5. (a) Breuilles, P.; Uguen, D. *Tetrahedron Lett.* **1998**, *39*, 3149–3152; (b) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281–5284; (c) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179–3181.
6. Mikami, K.; Ohmura, H. *Org. Lett.* **2002**, *4*, 3355–3357.
7. (a) Cosp, A.; Llacer, E.; Romea, P.; Urpí, F. *Tetrahedron Lett.* **2006**, *47*, 5819–5823; (b) Cosp, A.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **2001**, *42*, 4629–4631.
8. To prove the stereochemistry of adduct, compound **9** was converted to compound **29**. The spectral data of **29** matched with the reported data.[9]



Reagents and conditions: (i) $NaBH_4$, EtOH, rt, 45 min, 92%; (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 10 min, 96%; (iii) OsO_4, acetone–H_2O (8:1), rt, 4 h; then $NaIO_4$, THF: pH 7 buffer (1:1), 0 °C to rt, 10 min, 90%; (iv) $NaBH_4$, MeOH, rt, 15 min, 92%.

9. Makoto, K.; Mitsuru, S.; Masahiro, Y.; Kozo, S. *Synthesis* **2009**, 2893–2904.
10. Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391–2393.
11. Patel, J.; Clave, G.; Renard, P. Y.; Frank, X. *Angew. Chem. Int. Ed.* **2008**, *47*, 4224–4227.
12. (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561–564; (b) Muller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521–522.
13. Analytical and spectral data/Selected physical data of compound **5**: $R_f = 0.6$ (SiO_2, 10% EtOAc in petroleum ether); $[\alpha]_D^{28} = +36.8$ (*c* 0.156, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.03 (s, 3H), 0.06 (s, 3H), 0.81–0.92 (m, 21H), 1.25–1.37 (m, 9H), 1.42–1.55 (m, 6H), 1.63 (ddd, *J* = 14.1, 6.4, 5.2 Hz, 1H), 1.84 (ddd, *J* = 14.1, 7.9, 5.2 Hz, 1H), 2.48 (dd, *J* = 14.8, 7.5 Hz, 1H), 2.55 (dd, *J* = 14.8, 5.4 Hz, 1H), 3.23 (s, 3H), 3.56–3.70 (m, 4H), 4.3 (m, 1H), 5.75 (dd, *J* = 19.1, 7.1 Hz, 1H), 6.12 (d, *J* = 19.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.1, 148.2, 131.7, 82.3, 66.9, 55.9, 51.3, 43.2, 42.5, 29.1, 27.2, 25.7, 17.9, 13.6, 9.5, −4.5, −4.8; IR (KBr): ν_{max} 2927, 2856, 1735, 1590, 1461, 1373, 1217, 1093, 766 cm^{-1}; MS (ESI): *m*/*z* (%) 592.2 (70) $[M+H]^+$.
14. Ramana Rao, M. H. V.; Kiran Kumar, S.; Kunwar, A. C. *Tetrahedron Lett.* **2003**, *44*, 7369–7372.
15. Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165–1168.
16. Williams, D. R.; Lowder, P. D.; Gu, Y. G.; Brooks, D. A. *Tetrahedron Lett.* **1997**, *38*, 331–334.
17. Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467–8468.
18. Grandjean, D.; Pale, P.; Chuche, J. *Tetrahedron Lett.* **1994**, *35*, 3529–3530.
19. Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857–1867.
20. Analytical and spectral data/Selected physical data of compound **6**: $R_f = 0.5$ (SiO_2, 50% EtOAc in petroleum ether); $[\alpha]_D^{28} = -16.0$ (*c* 0.368, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 2.56 (t, *J* = 6.7 Hz, 2H), 3.47 (br s, 1H), 3.30 (s, 3H), 4.21 (t, *J* = 6.2 Hz, 1H), 4.73 (s, 2H), 6.11 (d, *J* = 14.4 Hz, 1H), 6.49 (dt, *J* = 14.4, 7.3 Hz, 1H), 7.54 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.1, 141.3, 139.7, 136.0, 77.6, 74.8, 57.1, 56.8, 40.6; IR (KBr): ν_{max} 3358, 3157, 2922, 2855, 1655, 1584, 1460, 1218, 768 cm^{-1}; MS (ESI): *m*/*z* (%) 310.1 (100) $[M+H]^+$.
21. Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813–817.
22. Analytical and spectral data/Selected physical data of compound **3**: $R_f = 0.4$ (SiO_2, 50% EtOAc in petroleum ether); $[\alpha]_D^{28} = +24.6$ (*c* 0.16, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 0.02 (s, 3H), 0.04 (s, 3H), 0.86 (s, 9H), 1.62 (ddd, *J* = 14.1, 6.4, 5.2 Hz, 1H), 1.83 (ddd, *J* = 14.1, 7.7, 5.2 Hz, 1H), 2.45–2.55 (m, 3H), 2.63 (t, *J* = 6.5 Hz, 2H), 3.21 (s, 3H), 3.34 (s, 3H), 3.56–3.70 (m, 4H), 4.20–4.28 (m, 2H), 4.73 (s, 2H), 5.39 (dd, *J* = 14.2, 7.9 Hz, 1H), 5.65 (dt, *J* = 14.32, 7.23 Hz, 1H), 6.05–6.16 (m, 2H), 7.54 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 172.2, 163.5, 140.4, 136.2, 132.5, 132.1, 131.9, 129.7, 78.6, 76.0, 75.3, 66.7, 57.6, 56.9, 51.4, 43.3, 42.3, 37.8, 25.7, 17.9, −4.4, −4.8; IR (KBr): ν_{max} 3420, 3143, 2922, 2854, 1732, 1658, 1581, 1461, 1461, 1372, 1218, 768 cm^{-1}; HRMS (ESI): calcd for $C_{24}H_{41}NO_7NaSi$ $[M+Na]^+$: 506.2544, found 506.2557 $[M+Na]^+$.